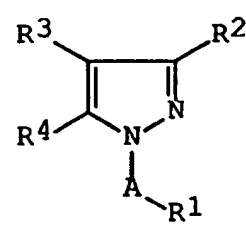


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<p>(54) Title: 5-ARYLPYRAZOLE COMPOUNDS</p> <p>(57) Abstract</p> <p>A compound of formula (I), wherein R<sup>1</sup> is aryl optionally substituted with substituent(s) selected from the group consisting of halogen, nitro, amino, esterified carboxy, carboxy, carbamoyl, cyano and lower alkoxy, R<sup>2</sup> is hydrogen, amino, halogen, esterified carboxy, carboxy, carbamoyl, cyano, or lower alkyl substituted with halogen, R<sup>3</sup> is hydrogen, aryl optionally substituted with halogen, or lower alkyl optionally substituted with hydroxy, amino or carboxy, R<sup>4</sup> is aryl substituted with substituent(s) selected from the group consisting of halogen, lower alkoxy, lower alkylthio, lower alkylsulfinyl, lower alkylsulfonyl, sulfamoyl, and lower alkylsulfamoyl, and A is lower alkylene, and its salt, which are useful as medicament.</p> <div style="text-align: center;">  <p>(I)</p> </div> <div style="text-align: right; margin-top: 200px;"> <p>Atty. Docket No. 6794S-5/US/USC Serial No. 10/031,898 Kararli, et al. Reference 22 of 69</p> </div>		

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## D E S C R I P T I O N

5-ARYLPYRAZOLE COMPOUNDS5     Technical Field

      This invention relates to 5-arylpyrazole compounds having pharmacological activity, to a process for their production and to a pharmaceutical composition containing the same.

10

Background Art

      Some pyrazole derivatives having antiinflammatory and/or analgesic activities have been known, for example, in Canadian Patent 1 130 808, and EP Patent Publication Nos. 248 594, 272 704, 293 220, 418 845 and 554 829, and WO Patent Publication Nos. 95/15315, 95/15316, 95/15317, 95/15318, 96/14302 and 97/15271.

15

Disclosure of Invention

20

      This invention relates to 5-arylpyrazole compounds, which have pharmaceutical activity such as cyclooxygenase-2 (hereinafter described as COX-II) inhibiting activity, to a process for their production, to a pharmaceutical composition containing the same and to a use thereof.

25

      Accordingly, one object of this invention is to provide the 5-arylpyrazole compounds, which have a COX-II inhibiting activity.

      Another object of this invention is to provide a process for production of the 5-arylpyrazole compounds.

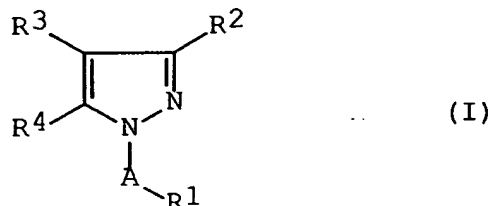
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      A further object of this invention is to provide a pharmaceutical composition containing, as active ingredients, the 5-arylpyrazole compounds.

35

      Still further object of this invention is to provide a use of the 5-arylpyrazole compounds for manufacturing a medicament for treating or preventing various diseases.

The new 5-arylpyrazole compounds of this invention can be represented by the following general formula (I):



10 wherein R<sup>1</sup> is aryl optionally substituted with substituent(s) selected from the group consisting of halogen, nitro, amino, esterified carboxy, carboxy, carbamoyl, cyano and lower alkoxy,  
R<sup>2</sup> is hydrogen, amino, halogen, estrified carboxy, carboxy, carbamoyl, cyano, or lower alkyl  
15 substituted with halogen,  
R<sup>3</sup> is hydrogen, aryl optionally substituted with halogen, or lower alkyl optionally substituted with hydroxy, amino or carboxy,  
R<sup>4</sup> is aryl substituted with substituent(s) selected  
20 from the group consisting of halogen, lower alkoxy, lower alkylthio, lower alkylsulfinyl, lower alkylsulfonyl, sulfamoyl, and lower alkylsulfamoyl, and  
A is lower alkylene,  
25 and its salt.

30 The compounds of formula (I) may contain one or more asymmetric centers and thus they can exist as enantiomers or diastereoisomers. This invention includes both mixtures and separate individual isomers.

The compounds of the formula (I) may also exist in tautomeric forms and the invention includes both mixtures and separate individual tautomers.

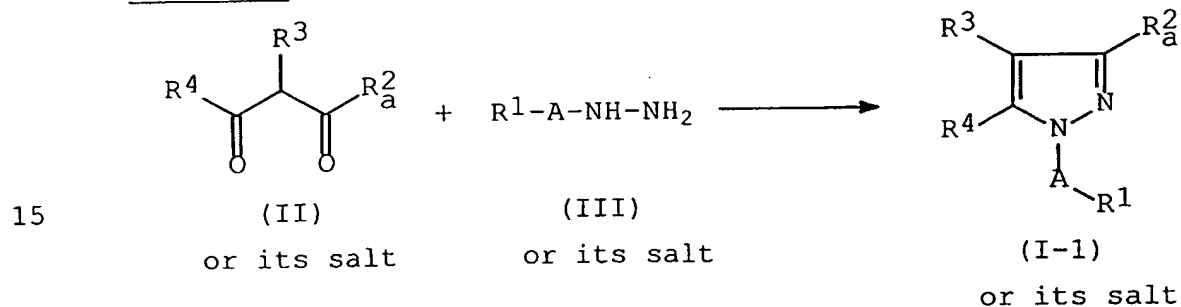
35 The compound of the formula (I) and its salt can be in a form of a solvate, which is included within the scope of the

present invention. The solvate preferably include a hydrate and an ethanolate.

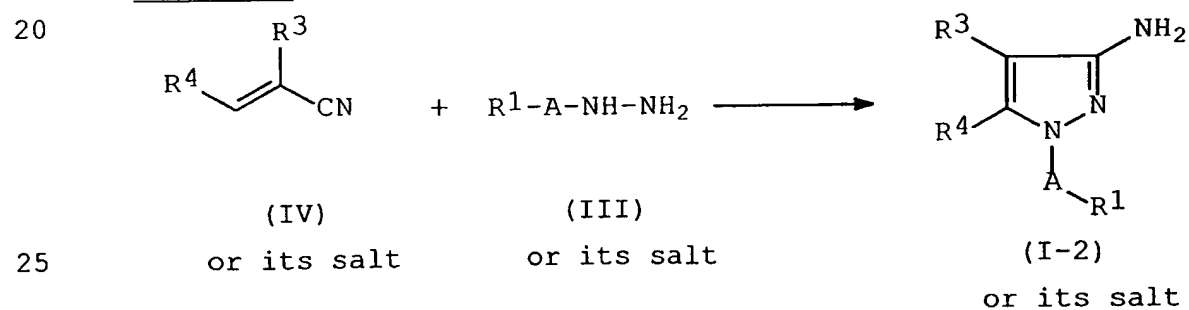
Also included in the scope of invention are radiolabelled derivatives of compounds of formula (I) which are suitable for biological studies.

The object compound (I) or its salt can be prepared by the following process.

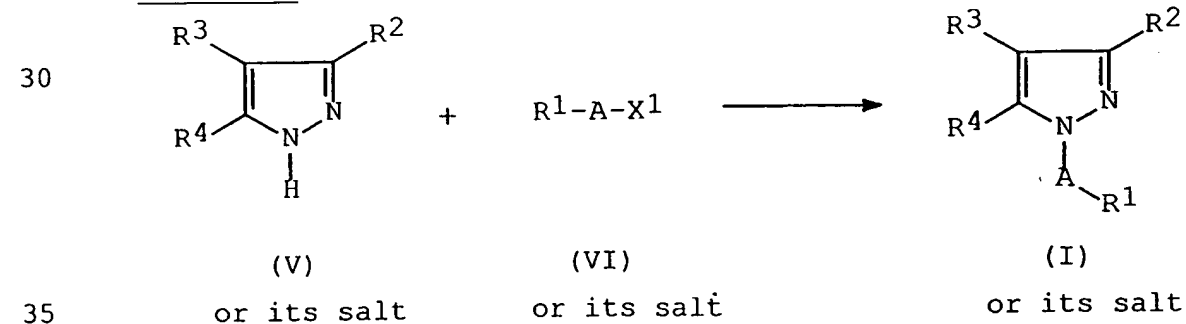
10 Process 1



20 Process 2

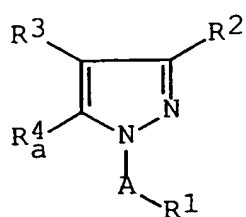


30 Process 3



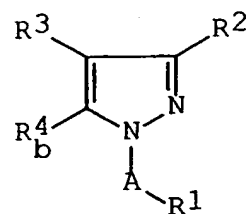
Process 4

5



(I-3)

or its salt

Oxidation  
→

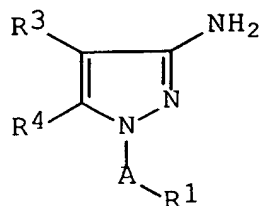
(I-4)

or its salt

10

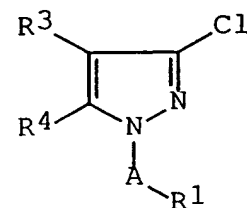
Process 5

15



(I-5)

or its salt

Chlorination  
→

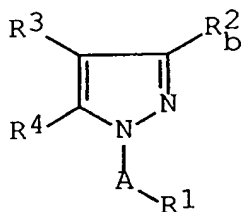
(I-6)

or its salt

20

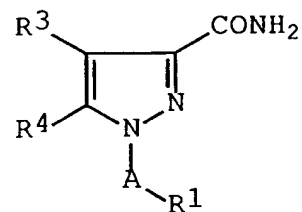
Process 6

25



(I-7)

or its salt

Amidation  
→

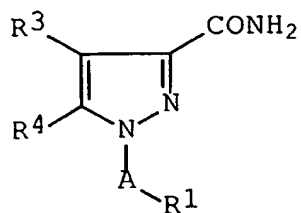
(I-8)

or its salt

30

Process 7

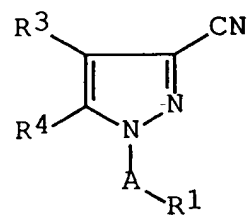
35



(I-9)

or its salt

→



(I-10)

or its salt

wherein  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$  and A are each as defined above,

$R_a^2$  is hydrogen, esterified carboxy, carbamoyl,  
cyano, or lower alkyl substituted with  
halogen,

5  $R_b^2$  is esterified carboxy or carboxy,

$R_a^4$  is aryl substituted with lower alkylthio,

$R_b^4$  is aryl substituted with lower alkylsulfinyl or  
lower alkylsulfonyl, and

$X^1$  is a leaving group.

10

In the above and subsequent description of the present  
specification, suitable examples of the various definitions  
to be included within the scope of the invention are  
explained in detail in the following.

15

The term "lower" is intended to mean a group having 1 to  
6 carbon atom(s), unless otherwise provided.

Suitable "lower alkyl" and lower alkyl moiety in the  
terms "lower alkylthio", "lower alkylsulfinyl", "lower  
20 alkylsulfonyl", "lower alkylsulfamoyl" and "lower alkoxy" may  
be a straight or branched one, such as methyl, ethyl, propyl,  
isopropyl, butyl, isobutyl, tert-butyl, pentyl, hexyl, or the  
like, in which preferable one is methyl.

Suitable "lower alkyl substituted with halogen" may be  
25 difluoromethyl, trifluoromethyl, or the like.

Suitable "lower alkylene" may be straight or branched  
one having 1 to 6 carbon atom(s), such as methylene,  
ethylene, trimethylene, hexamethylene, or the like,  
preferably one having 1 to 3 carbon atom(s), more preferably  
30 methylene.

Suitable "halogen" may be fluoro, chloro, bromo or iodo.

Suitable "aryl" may be phenyl, naphthyl, tolyl, xylyl,  
ethylphenyl, propylphenyl, or the like.

Suitable "esterified carboxy" may be substituted or  
35 unsubstituted lower alkoxycarbonyl [e.g., methoxycarbonyl,

ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, 2,2,2-trichloroethoxycarbonyl, etc.], substituted or unsubstituted aryloxy carbonyl [e.g., phenoxy carbonyl, 4-nitrophenoxy carbonyl, etc.], substituted or unsubstituted ar(lower)alkoxy carbonyl [e.g. benzyloxy carbonyl, 4-nitorobenzyloxy carbonyl, etc.], or the like.

Suitable "leaving group" may be halogen, acyloxy [e.g., acetyloxy, trifluoroacetyloxy, etc.], lower alkylsulfonyloxy [e.g., methanesulfonyloxy, etc.], triarylphosphinoxy [e.g., -O-P<sup>+</sup>(C<sub>6</sub>H<sub>5</sub>)<sub>3</sub>, etc.], or the like.

Suitable salts of the compounds (I) and (I-1) to (I-10), and the compounds (II) to (VI) are pharmaceutically acceptable conventional non-toxic salts and include a metal salt such as an alkali metal salt (e.g., sodium salt, potassium salt, etc.) and an alkaline earth metal salt (e.g., calcium salt, magnesium salt, etc.), an ammonium salt, an organic base salt (e.g., trimethylamine salt, triethylamine salt, pyridine salt, picoline salt, dicyclohexylamine salt, etc.), an organic acid salt (e.g., acetate, maleate, tartrate, methanesulfonate, benzenesulfonate, formate, toluenesulfonate, trifluoroacetate, etc.), an inorganic acid salt (e.g., hydrochloride, hydrobromide, sulfate, phosphate, etc.), a salt with an amino acid (e.g., arginine, aspartic acid, glutamic acid, etc.), or the like.

The processes for preparing the object compound (I) are explained in detail in the following.

#### 30 Process 1

The compound (I-1) or its salt can be prepared by reacting the compound (II) or its salt with a hydrazine derivative (III) or its salt.

The reaction is usually carried out in a conventional solvent such as water, alcohol [e.g., methanol, ethanol,



isopropyl alcohol, etc.], alkanolic acid, tetrahydrofuran, dioxane, toluene, methylene chloride, chloroform, N,N-dimethylformamide, or any other organic solvents which do not adversely affect the reaction, or the mixture thereof, preferably, acidic solvent such as alkanolic acid (e.g., acetic acid).

The reaction temperature is not critical and the reaction is usually carried out under cooling to warming.

#### 10 Process 2

The compound (I-2) or its salt can be prepared by reacting the compound (IV) or its salt with the compound (III) or its salt.

This reaction can be carried out in a similar manner to that of Process 1, and therefore the reaction conditions (e.g., solvent, reaction temperature, etc.) can be referred to those of the Process 1.

#### Process 3

20 The compound (I) or its salt can be prepared by reacting the compound (V) or its salt with the compound (VI) or its salt.

This reaction is usually carried out in the presence of an inorganic or an organic base.

25 Suitable inorganic base may include an alkali metal [e.g., sodium, potassium, etc.], an alkali metal hydroxide [e.g., sodium hydroxide, potassium hydroxide, etc.], alkali metal hydrogen carbonate [e.g., sodium hydrogen carbonate, potassium hydrogen carbonate, etc.], alkali metal carbonate [e.g., sodium carbonate, etc.], alkali earth metal carbonate [calcium carbonate, etc.], or the like.

30 Suitable organic base may include tri(lower)alkylamine [e.g. triethylamine, N,N-diisopropylethylamine, etc.], alkyl lithium [e.g. methyl lithium, butyl lithium, etc.], lithium diisopropylamide, lithium hexamethyldisirazido, alkali metal

hydride [e.g., sodium hydride, potassium hydride, etc.] or the like.

The reaction is usually carried out in a conventional solvent such as water, alcohol [e.g., methanol, ethanol, isopropyl alcohol, etc.], tetrahydrofuran, dioxane, toluene, methylene chloride, chloroform, N,N-dimethylformamide or any other organic solvents which do not adversely affect the reaction, or the mixture thereof.

The reaction temperature is not critical and the reaction is usually carried out under cooling to warming.

#### Process 4

The compound (I-4) or its salt can be prepared by reacting a compound (I-3) or its salt with an oxidizing agent.

The suitable oxidizing agent may be hydrogen peroxide, cumene hydroperoxide, tert-butyl hydroperoxide, Jones reagent, peracid [e.g. peracetic acid, perbenzoic acid, m-chloroperbenzoic acid, monopersulfate compound (oxone<sup>®</sup>), etc.], chromic acid, potassium permanganate, alkali metal periodate [e.g. sodium periodate, etc.], and the like.

This reaction is usually carried out in a solvent which does not adversely influence the reaction such as acetic acid, dichloromethane, acetone, ethyl acetate, chloroform, water, an alcohol [e.g. methanol, ethanol, etc.], a mixture thereof or the like.

The reaction temperature is not critical, and the reaction is usually carried out under cooling to warming.

#### Process 5

The compound (I-6) or its salt can be prepared from the compound (I-5) or its salt by the following methods.

Namely, 1) the compound (I-5) or its salt is firstly reacted with a nitrite compound, and then 2) the resulting product is reacted with cuprous chloride.

Suitable nitrite compound may be alkali metal nitrite [e.g. sodium nitrite, potassium nitrite, etc.], alkyl nitrite [e.g. isoamyl nitrate, tert-butyl nitrite, etc.], and the like.

5        In the first step, the reaction is preferably carried out in the presence of an acid [e.g. hydrochloric acid sulfuric acid, etc.].

10       The reaction is usually carried out in a solvent such as water, tetrahydrofuran, dioxane, acetonitrile, or any other organic solvent which does not adversely influence the reaction, or a mixture thereof.

The reaction temperature is not critical and the reaction can be carried out under cooling to warming.

15       In the second step, the reaction is preferably carried out in the presence of alkali metal halide [e.g. sodium chloride, etc.] and an inorganic acid [e.g. hydrochloric acid, etc.].

20       The reaction is usually carried out in a solvent such as water, tetrahydrofuran, dioxane, or any other organic solvent which does not adversely influence the reaction, or a mixture thereof.

The reaction temperature is not critical and the reaction can be carried out warming to heating.

#### 25       Process 6

The compound (I-8) or its salt can be prepared by subjecting the compound (I-7) or its salt to amidation reaction.

30       Amidation reaction can be carried out in a conventional manner, which is capable of converting carboxy group or protected carboxy group to carbamoyl group. Amidation can preferably carried out by, for example, (i) reacting the compound (I-7), wherein  $R_D^2$  is esterified carboxy, with alkanoylamine (e.g., aceamide, formamide, etc.) in the  
35       presence of organic base (e.g., sodium alkoxide, etc.) or

(ii) reacting the compound (I-7), wherein  $R_B^2$  is carboxy, or its salt, with ammonia or its salt in the presence of condensing agent.

5 The reaction is usually carried out in a conventional solvent such as alcohol [e.g., methanol, ethanol, isopropyl alcohol, etc.], tetrahydrofuran, dioxane, toluene, methylene chloride, chloroform, N,N-dimethylformamide, or any other organic solvents which do not adversely affect the reaction, or the mixture thereof.

10 The reaction temperature is not critical and the reaction is usually carried out under cooling to warming.

#### Process 7

15 The compound (I-10) or its salt can be prepared by subjecting the compound (I-9) or its salt to dehydration reaction.

Dehydration reaction can be carried out in the conventional manner, which is capable of dehydrating a carbamoyl group to cyano group, and suitable dehydrating agent may be phosphorus compound (e.g., phosphorus  
20 oxychloride, etc.) or the like.

The reaction is usually carried out in a conventional solvent such as alcohol [e.g., methanol, ethanol, isopropyl alcohol, etc.], tetrahydrofuran, dioxane, toluene, methylene  
25 chloride, chloroform, N,N-dimethylformamide, or any other organic solvents which do not adversely affect the reaction, or the mixture thereof.

The reaction temperature is not critical and the reaction is usually carried out under cooling to warming.

30

Suitable organic base may be tri(lower)alkylamine [e.g., triethylamine, N,N-diisopropylethylamine, etc.], alkyl magnesium bromide [e.g., methyl magnesium bromide, ethyl magnesium bromide, etc.], alkyl lithium [e.g., methyl  
35 lithium, butyl lithium, etc.], lithium diisopropylamide,

lithium hexamethyldisirazido, or the like.

The reaction is usually carried out in a conventional solvent such as water, alcohol [e.g., methanol, ethanol, isopropyl alcohol, etc.], tetrahydrofuran, dioxane, toluene, methylene chloride, chloroform, N,N-dimethylformamide, or any other organic solvents which do not adversely affect the reaction, or the mixture thereof.

The reaction temperature is not critical and the reaction is usually carried out under cooling to warming.

10

The object compound (I) or pharmaceutically acceptable salts thereof of this invention possesses COX-II inhibiting activity and possesses strong antiinflammatory, antipyretic, analgesic, antithrombotic, anti-cancer activities, and so on. The object compound (I) and pharmaceutically acceptable salt thereof, therefore, are useful for treating and/or preventing COX-II mediated diseases, inflammatory conditions, various pains, collagen diseases, autoimmune diseases, various immunological diseases, thrombosis, cancer and neurodegenerative diseases in human beings or animals by using administered systemically or topically. More particularly, the object compound (I) and pharmaceutically acceptable salts thereof are useful for treating and/or preventing inflammation and pain in joint and muscle [e.g. rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis, juvenile arthritis, etc.], inflammatory skin condition [e.g. sunburn, burns, eczema, dermatitis, etc.], inflammatory eye condition [e.g. conjunctivitis, etc.], lung disorder in which inflammation is involved [e.g. asthma, bronchitis, pigeon fancier's disease, farmer's lung, etc.], condition of the gastrointestinal tract associated with inflammation [e.g. aphthous ulcer, Chrohn's disease, atopic gastritis, gastritis varialoforme, ulcerative colitis, coeliac disease, regional ileitis, irritable bowel syndrome, etc.], gingivitis, inflammation, pain and tumescence after

35

operation or injury, pyrexia, pain and other conditions associated with inflammation, particularly those in which lipoxxygenase and cyclooxygenase products are a factor, systemic lupus erythematosus, scleroderma, polymyositis, tendinitis, bursitis, periarteritis nodose, rheumatic fever, Sjögren's syndrome, Behcet disease, thyroiditis, type I diabetes, nephrotic syndrome, aplastic anemia, myasthenia gravis, uveitis contact dermatitis, psoriasis, Kawasaki disease, sarcoidosis, Hodgkin's disease, Alzheimers disease, or the like. Additionally, the object compound (I) or a salt thereof is expected to be useful as therapeutical and/or preventive agents for cardiovascular or cerebrovascular diseases, the diseases caused by hyperglycemia and hyperlipemia.

The patents, patent applications and publications cited herein are incorporated by reference.

In order to illustrate the usefulness of the object compound (I), the pharmacological test data of the compound (I) are shown in the following.

[A] ANTIINFLAMMATORY ACTIVITY :

Effect on adjuvant arthritis in rats :

(i) Test Method :

Ten female Sprague-Dawley rats were used per group. A dose of 0.5 mg of Mycobacterium tuberculosis (strain M37 BA) suspended in 0.05 ml of liquid paraffin was injected subcutaneously in the right hind paw. The injection of mycobacterial adjuvant produced local inflammatory lesions (primary lesion) and then about 10 days later, secondary lesions in both the injected and uninjected paws. The

volumes of both paws before and on days 23 after the injection was measured as percent inhibition in comparison to vehicle-treated controls. The drug was given orally once a day for 23 consecutive days from day 1 after the injection.

5

(ii) Test Results :

Test compound (Example No.)	Dose (mg/kg)	Inhibition of secondary lesion (uninjected paw) (%)
3	1.0	>60

10

[B] COX-I and COX-II activity in vitro :

(i) Test Method :

15

Cyclooxygenase activities in the absence or presence of inhibitors were measured by determining the level of prostaglandin E<sub>2</sub> (PGE<sub>2</sub>) synthesis from arachidonic acid. Enzymes (1 µg for COX-I and/or 3 µg for COX-II) in a total volume of 200 µl of reaction buffer were incubated in the absence or presence of various concentrations of inhibitors for 5 minutes at 30°C. The reaction was then started by the addition of arachidonic acid to the final concentration of 10 µM. The reaction was terminated by 50 µl of 1N-HCl after incubation at 30°C for 5 minutes. PGE<sub>2</sub> was extracted with ethyl acetate, concentrated under a stream of nitrogen and analyzed by a radio immunoassay kit (Amersham) according to the manufacture's instructions.

20

25

COX inhibiting activity of the test compound was assayed as PGE<sub>2</sub> formation using radioimmunoassay to detect a prostaglandin release. The appropriate COX enzyme was incubated in 0.1 M Tris-HCl buffer (pH 7.3) containing hematin and tryptophan with the addition of arachidonic acid (10 µM) for 5 minutes at 37°C. Compounds were pre-incubated

30

with the enzyme for 5 minutes prior to the addition of arachidonic acid. Any reaction between the arachidonic acid and the enzyme was stopped after 5 minutes at 37°C by addition of 20 µl of 1N HCl. PGE<sub>2</sub> formation was measured by radioimmunoassay (Amersham).

It appeared, from the below-mentioned Test Results, that the compound (I) or pharmaceutically acceptable salts thereof of the present invention have a selective inhibiting activity against COX-II.

(ii) Test Results :

Test Compound (Example No.)	Human COX-I IC <sub>50</sub> (µM)	Sheep COX-II IC <sub>50</sub> (µM)
4-(2)	>100	< 1
5-(4)	> 15	< 1

For therapeutic purpose, the compound (I) and a pharmaceutically acceptable salt thereof of the present invention can be used in a form of pharmaceutical preparation containing one of said compounds as an active ingredient, in admixture with a pharmaceutically acceptable carrier such as an organic or inorganic solid or liquid excipient suitable for oral, parenteral or external administration. The pharmaceutical preparations may be capsules, tablets, dragees, granules, inhalant, suppositories, solution, lotion, suspension, emulsion, ointment, gel, or the like. If desired, there may be included in these preparations, auxiliary substances, stabilizing agents, wetting or emulsifying agents, buffers and other commonly used additives.

While the dosage of therapeutically effective amount of the compound (I) will vary depending upon the age and



condition of each individual patient, an average single dose of about 0.01 mg, 0.1 mg, 1 mg, 10 mg, 50 mg, 100 mg, 250 mg, 500 mg and 1000 mg of the compound (I) may be effective for treating the above-mentioned diseases. In general, amounts  
5 between 0.01 mg/body and about 1,000 mg/body may be administered per day.

The following Preparation and Examples are given for the purpose of illustrating the present invention in detail.  
10

Preparation 1

Sodium hydride (60 %, 1.34 g) was added to a solution of 4-acetylbenzenesulfonamide (1.99 g) and ethyl trifluoroacetate (3.26 g) in dimethylformamide (20 ml) at 10-15°C. The resultant mixture was stirred at room temperature for 1 hour and poured into a mixture of ethyl acetate and 1N-hydrogen chloride solution. The organic layer was washed with saturated sodium hydrogen carbonate, and brine successively, dried, and concentrated to dryness. The residue was triturated with isopropyl ether to afford 4-(4,4,4-trifluoro-3-oxo-butyryl)benzenesulfonamide (0.95 g) as a pale yellow crystals.

mp : 142-144 °C

IR (KBr) : 1778, 1602, 1565, 1457 cm<sup>-1</sup>

NMR (DMSO-d<sub>6</sub>, δ) : 2.52 (3H, s), 7.03 (1H, s), 7.50-8.02 (7H, m)

Preparation 2

A mixture of 3',4'-difluoroacetophenone (23.8 g) and sodium thiomethoxide (95 %, 12.4 g) in acetonitrile (720 ml) was stirred at room temperature for 4 hours and warmed at 50°C for 2 hours. The reaction mixture was poured into a mixture of ethyl acetate and water. The organic layer was washed with water, and brine successively, dried, and concentrated to dryness. The residue was triturated with n-hexane to afford 3'-fluoro-4'-(methylthio)acetophenone (17.5 g) as a pale yellow crystals.

mp : 70-72 °C

IR (KBr) : 1673, 1596, 1558, 1403 cm<sup>-1</sup>

NMR (DMSO-d<sub>6</sub>, δ) : 2.52 (3H, s), 3.33 (3H, s), 7.50-7.90 (3H, m)

Preparation 3

The following compound was prepared in a similar manner to that of Preparation 1.

4,4,4-Trifluoro-1-[3-fluoro-4-(methylthio)phenyl]-  
butane-1,3-dione

pale yellow crystals

mp : 60-63 °C

5 IR (KBr) : 1641, 1602, 1548, 1464  $\text{cm}^{-1}$

NMR ( $\text{CDCl}_3$ ,  $\delta$ ) : 2.54 (3H, s), 6.51 (1H, s), 7.50-  
7.90 (3H, m)

#### Preparation 4

10 The following compound was prepared in a similar  
manner to that of Example 2.

4,4,4-Trifluoro-1-[3-fluoro-4-(methylsulfonyl)-  
phenyl]butane-1,3-dione

pale yellow crystals

15 mp : 109-110 °C

IR (KBr) : 1689, 1683, 1571, 1411  $\text{cm}^{-1}$

NMR ( $\text{CDCl}_3$ ,  $\delta$ ) : 3.27 (3H, s), 6.58 (1H, s), 7.80-  
8.20 (3H, m)

#### Example 1

20 A mixture of 4,4,4-trifluoro-1-[4-(methylthio)-  
phenyl]butane-1,3-dione (405 mg) and 4-chlorobenzyl-  
hydrazine (300 mg) in acetic acid (5 ml) was refluxed for 1  
hour. The solvent was evaporated under reduced pressure  
25 and ethyl acetate and water were added to the residue. The  
organic layer was washed with saturated sodium hydrogen  
carbonate, and brine successively, dried, and concentrated  
to dryness. The residue was chromatographed (toluene) over  
silica gel to afford 1-(4-chlorobenzyl)-5-[4-(methylthio)-  
30 phenyl]-3-(trifluoromethyl)pyrazole (0.35 g) as a pale  
yellow oil.

IR (neat) : 1621, 1590, 1490  $\text{cm}^{-1}$

NMR ( $\text{CDCl}_3$ ,  $\delta$ ) : 2.51 (3H, s), 3.80 (2H, s), 6.06  
(1H, s), 7.00-8.00 (8H, m)

35 MS : 383  $[\text{M}+\text{H}]^+$

Example 2

m-Chloroperbenzoic acid (80%, 360 mg) was added to a solution of 1-(4-chlorobenzyl)-5-[4-(methylthio)phenyl]-3-(trifluoromethyl)pyrazole (260 mg) in methylene chloride (20 ml) at 0-5°C. The reaction mixture was stirred for 1 hour, and then washed with saturated sodium hydrogen carbonate, and brine successively, and dried. After removal of the solvent, the residue was chromatographed (toluene : ethyl acetate = 5 : 1) over silica gel to afford 1-(4-chlorobenzyl)-5-[4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)pyrazole (60 mg) as a white crystals.

mp : 112-115 °C

IR (KBr) : 1693, 1496, 1409 cm<sup>-1</sup>

NMR (CDCl<sub>3</sub>, δ) : 3.09 (3H, s), 5.34 (2H, s), 6.67 (1H, s), 6.80-7.40 (4H, m), 7.36 (2H, d, J=8Hz), 8.02 (2H, d, J=8Hz)

MS : 415(M<sup>+</sup>), 417(M<sup>+2</sup>)

Example 3

A mixture of 4,4,4-trifluoro-1-[4-(methylsulfonyl)-phenyl]butane-1,3-dione (1.3 g) and 3-fluorobenzylhydrazine (774 mg) in acetic acid (15 ml) was refluxed for 2 hours.

The solvent was evaporated under reduced pressure, and ethyl acetate and water were added to the residue. The organic layer was washed with saturated sodium hydrogen carbonate, and brine successively, dried, and concentrated to dryness. The residue was recrystallized from ethanol to afford 1-(3-fluorobenzyl)-5-[4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)pyrazole (0.76 g) as a white crystals.

mp : 120-122 °C

IR (KBr) : 1594, 1496, 1479 cm<sup>-1</sup>

NMR (CDCl<sub>3</sub>, δ) : 3.10 (3H, s), 5.37 (2H, s), 6.69 (1H, s), 6.70-7.20 (4H, m), 7.49 (2H, d, J=8Hz), 8.00 (2H, d, J=8Hz)

MS : 399 [M+H]<sup>+</sup>

Example 4

5 The following compounds described in (1)-(2) were prepared in a similar manner to that of Example 1.

(1) 1-(4-Fluorobenzyl)-5-[4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)pyrazole

white crystals

10 mp : 140-142 °C

IR (KBr) : 1608, 1509, 1467 cm<sup>-1</sup>

NMR (CDCl<sub>3</sub>, δ) : 3.10 (3H, s), 5.34 (2H, s), 6.69 (1H, s), 6.90-7.30 (4H, m), 7.49 (2H, d, J=8Hz), 8.01 (2H, d, J=8Hz)

15 MS : 399 [M+H]<sup>+</sup>

(2) 1-Benzyl-5-[4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)pyrazole

white crystals.

20 mp : 123-125 °C

IR (KBr) : 1606, 1502, 1463 cm<sup>-1</sup>

NMR (CDCl<sub>3</sub>, δ) : 3.08 (3H, s), 5.39 (2H, s), 6.68 (1H, s), 6.90-7.40 (4H, m), 7.48 (2H, d, J=8Hz), 7.98 (2H, d, J=8Hz)

25 MS : 381 [M+H]<sup>+</sup>

Anal. Calcd. for C<sub>18</sub>H<sub>15</sub>F<sub>3</sub>N<sub>2</sub>O<sub>2</sub>S :

C, 56.84; H, 3.97; N, 7.36

Found. C, 56.44; H, 3.89; N, 7.19

30 Example 5

The following compounds described in (1)-(7) were prepared in a similar manner to that of Example 3.

(1) 1-(2-Fluorobenzyl)-5-[4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)pyrazole

35

white crystals

mp : 136-138 °C

IR (KBr) : 1605, 1595, 1461  $\text{cm}^{-1}$

NMR ( $\text{CDCl}_3$ ,  $\delta$ ) : 3.10 (3H, s), 5.43 (2H, s), 6.69  
5 (1H, s), 6.90-7.40 (4H, m), 7.51 (2H, d,  $J=8\text{Hz}$ ),  
8.00 (2H, d,  $J=8\text{Hz}$ )

MS : 399  $[\text{M}+\text{H}]^+$

Anal. Calcd. for  $\text{C}_{18}\text{H}_{14}\text{F}_4\text{N}_2\text{O}_2\text{S}$  :

C, 54.27; H, 3.54; N, 7.03

10 Found. C, 54.39; H, 3.52; N, 7.02.

(2) 1-(2,4-Difluorobenzyl)-5-[4-(methylsulfonyl)phenyl]-  
3-(trifluoromethyl)pyrazole

white crystals

15 mp : 125-130 °C

IR (KBr) : 1612, 1508, 1467  $\text{cm}^{-1}$

NMR ( $\text{CDCl}_3$ ,  $\delta$ ) : 3.10 (3H, s), 5.37 (2H, s), 6.67  
(1H, s), 6.70-7.20 (3H, m), 7.52 (2H, d,  $J=8\text{Hz}$ ),  
8.02 (2H, d,  $J=8\text{Hz}$ )

20 MS : 417  $[\text{M}+\text{H}]^+$

Anal. Calcd. for  $\text{C}_{18}\text{H}_{13}\text{F}_5\text{N}_2\text{O}_2\text{S}$  :

C, 51.93; H, 3.15; N, 6.73

Found. C, 51.68; H, 3.10; N, 6.64

25 (3) 1-(1-Naphthylmethyl)-5-[4-(methylsulfonyl)phenyl]-3-  
(trifluoromethyl)pyrazole

white crystals

mp : 118-120 °C

IR (KBr) : 1600, 1506, 1465  $\text{cm}^{-1}$

30 NMR ( $\text{CDCl}_3$ ,  $\delta$ ) : 3.01 (3H, s), 5.89 (2H, s), 6.73  
(1H, s), 7.20-8.00 (11H, m)

MS : 431  $[\text{M}+\text{H}]^+$

Anal. Calcd. for  $\text{C}_{22}\text{H}_{17}\text{F}_3\text{N}_2\text{O}_2\text{S} \cdot 1/3\text{H}_2\text{O}$  :

C, 60.54; H, 3.93; N, 6.42

35 Found. C, 60.77; H, 4.01; N, 6.39

- (4) 4-[1-Benzyl-3-(trifluoromethyl)pyrazol-5-yl]benzene-sulfonamide  
white crystals  
mp : 80-85 °C  
5 IR (KBr) : 1714, 1563, 1463 cm<sup>-1</sup>  
NMR (CDCl<sub>3</sub>, δ) : 5.37 (2H, s), 6.66 (1H, s), 6.80-7.40 (5H, m), 7.43 (2H, d, J=8Hz), 7.97 (2H, d, J=8Hz)  
MS : 382 [M+H]<sup>+</sup>  
10 Anal. Calcd. for C<sub>17</sub>H<sub>14</sub>F<sub>3</sub>N<sub>3</sub>O<sub>2</sub>S :  
C, 53.54; H, 3.70; N, 11.02  
Found. C, 53.50; H, 3.90; N, 10.51
- (5) 1-Benzyl-5-[3-fluoro-4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)pyrazole  
15 white crystals  
mp : 118-120 °C  
IR (KBr) : 1623, 1565, 1498, 1460 cm<sup>-1</sup>  
NMR (CDCl<sub>3</sub>, δ) : 3.25 (3H, s), 5.40 (2H, s), 6.69  
20 (1H, s), 7.00-7.40 (7H, m), 7.99 (1H, m)  
MS : 399 [M+H]<sup>+</sup>
- (6) 1-Benzyl-5-[4-(methylsulfonyl)phenyl]-3-(difluoromethyl)pyrazole  
25 white crystals  
mp : 105-108 °C  
IR (KBr) : 1590, 1498, 1459 cm<sup>-1</sup>  
NMR (CDCl<sub>3</sub>, δ) : 3.08 (3H, s), 5.36 (2H, s), 6.65  
30 (1H, s), 6.50-7.40 (6H, m), 7.50 (2H, d, J=8Hz),  
7.98 (2H, d, J=8Hz)  
MS : 363 [M+H]<sup>+</sup>
- (7) Ethyl 1-(2,4-difluorobenzyl)-5-[4-(methylthio)phenyl]pyrazole-3-carboxylate  
35 pale yellow oil.

IR (neat) : 1742, 1610, 1504  $\text{cm}^{-1}$

NMR ( $\text{CDCl}_3$ ,  $\delta$ ) : 1.41 (3H, t,  $J=7\text{Hz}$ ), 2.50 (3H, s),  
4.43 (2H, q,  $J=7\text{Hz}$ ), 6.60-7.30 (8H, m)

MS : 389  $[\text{M}+\text{H}]^+$

5

#### Example 6

A mixture of sodium methoxide (3.0 g), benzyl-  
hydrazine (3.67 g) and 3-[4-(methylthio)phenyl]-  
acrylonitrile (5.00 g) in methanol was stirred at 140°C  
for 1 hour. The reaction mixture was extracted with  
methylene chloride and the organic layer was washed with  
water and brine successively, dried, and concentrated to  
dryness. The obtained materials and manganese(VI) dioxide  
( $\text{MnO}_2$ ) (10.0 g) in ethyl acetate (200 ml) were refluxed for  
2 hours. The reaction mixture was filtrated on celite and  
evaporated. The residue was chromatographed (toluene :  
ethyl acetate = 2 : 1) over silica gel to afford 1-benzyl-  
5-[4-(methylthio)phenyl]pyrazole-3-amine (0.98 g) as an  
orange crystals.

20

mp : 118-120 °C

IR (KBr) : 3432, 3351, 1602, 1548, 1504, 1459  $\text{cm}^{-1}$

NMR ( $\text{DMSO}-d_6$ ,  $\delta$ ) : 2.50 (3H, s), 5.23 (2H, s), 5.72  
(1H, s), 6.90-7.40 (9H, m)

MS : 296  $[\text{M}+\text{H}]^+$

25

#### Example 7

A solution of sodium nitrite (890 mg) was added to an  
ice-salt-cooled mixture of 1-benzyl-5-[4-(methylthio)-  
phenyl]pyrazole-3-amine (2.50 g) in concentrated  
hydrochloric acid (25 ml). The resultant mixture was  
stirred at 0°C for 30 minutes and added dropwise to a  
mixture of copper(I) chloride ( $\text{CuCl}$ ) (3.74 g) in  
concentrated hydrochloric acid (25 ml). The resultant  
mixture was stirred at room temperature and refluxed for 2  
hours. To the reaction mixture was added a mixture of

35



ethyl acetate and water. The organic layer was washed with saturated sodium hydrogen carbonate, and brine successively, dried, and concentrated to dryness. The residue was chromatographed (toluene) over silica gel to afford 1-benzyl-3-chloro-5-[4-(methylthio)phenyl]pyrazole (0.46 g) as a red oil.

IR (neat) : 1600, 1550, 1482, 1444  $\text{cm}^{-1}$

NMR ( $\text{CDCl}_3$ ,  $\delta$ ) : 2.50 (3H, s), 5.25 (2H, s), 6.24 (1H, s), 6.90-7.40 (9H, m)

MS : 315  $[\text{M}+\text{H}]^+$

#### Example 8

A mixture of sodium methoxide (324 mg) and ethyl 1-(2,4-difluorobenzyl)-5-[4-(methylsulfonyl)phenyl]pyrazole-3-carboxylate (840 mg) in formamide (5.0 ml) was warmed at 100°C for 1 hour. The reaction mixture was poured into ice-water and the precipitate was washed with water and ethanol to afford 1-(2,4-difluorobenzyl)-5-[4-(methylsulfonyl)phenyl]pyrazole-3-carboxamide (650 mg) as a white crystals.

mp : 205-208 °C

IR (KBr) : 3450, 3278, 3195, 1675, 1606, 1506, 1432  $\text{cm}^{-1}$

NMR ( $\text{CDCl}_3$ ,  $\delta$ ) : 3.10 (3H, s), 5.35 (2H, s), 5.5 (2H, bs), 6.70-7.10 (4H, m), 7.53 (2H, d,  $J=8\text{Hz}$ ), 8.02 (2H, d,  $J=8\text{Hz}$ )

MS : 392  $[\text{M}+\text{H}]^+$

#### Example 9

A mixture of methanesulfonyl chloride (1.05 g) and 1-(2,4-difluorobenzyl)-5-[4-(methylsulfonyl)phenyl]pyrazole-3-carboxamide (600 mg) in pyridine (5 ml) was warmed at 60°C for 2 hours. The reaction mixture was evaporated and ethyl acetate and water were added to the residue. The organic layer was washed with saturated

sodium hydrogen carbonate, and brine successively, dried, and concentrated to dryness. The residue was chromatographed (toluene : ethyl acetate = 5 : 1) over silica gel to afford 1-(2,4-difluorobenzyl)-5-[4-(methylsulfonyl)phenyl]pyrazole-3-carbonitrile (263 mg) as a white crystals.

mp : 103-104 °C

IR (KBr) : 2242, 1610, 1508, 1428 cm<sup>-1</sup>

NMR (CDCl<sub>3</sub>, δ) : 3.11 (3H, s), 5.35 (2H, s), 6.70-7.20 (4H, m), 7.53 (2H, d, J=8Hz), 8.05 (2H, d, J=8Hz)

MS : 374 [M+H]<sup>+</sup>

#### Example 10

Sodium hydride (60%, 338 mg) was added to a solution of 4-(4-fluorophenyl)-3-[4-(methylthio)phenyl]pyrazole (1.6 g) in dimethylformamide (30 ml) at 0°C. The resultant mixture was stirred at same temperature for 1 hour and benzylchloride (1.06 g) was dropwise to the above mixture. The reaction mixture was stirred for additional 2 hours at ambient temperature and poured into ice-water and extracted with ethyl acetate. The organic layer was washed with water, and brine successively, dried, and concentrated to dryness. The residue was chromatographed (CH<sub>2</sub>Cl<sub>2</sub> : n-hexane = 3 : 2) over silica gel to afford 1-benzyl-4-(4-fluorophenyl)-5-[4-(methylthio)phenyl]pyrazole (156 mg) from second fraction.

IR (nujol) : 1550, 1530, 1250 cm<sup>-1</sup>

NMR (DMSO-d<sub>6</sub>, δ) : 2.50 (3H, s), 5.02 (2H, s), 6.95-7.33 (13H, m), 7.89 (1H, s)

MS : 375 [M+H]<sup>+</sup>

#### Example 11

The following compounds described in (1)-(3) were prepared in a similar manner to that of Example 10.

(1) 1-(4-Chlorobenzyl)-4-(4-fluorophenyl)-5-[4-(methylthio)phenyl]pyrazole  
IR (nujol) : 1600, 1550  $\text{cm}^{-1}$   
NMR (DMSO- $\text{d}_6$ ,  $\delta$ ) : 2.50 (3H, s), 5.19 (2H, s), 6.70-7.43 (12H, m), 7.91 (1H, s)

(2) 4-(4-Fluorophenyl)-1-(4-nitrobenzyl)-5-[4-(methylthio)phenyl]pyrazole  
IR (nujol) : 1600, 1560, 1510  $\text{cm}^{-1}$   
NMR (DMSO- $\text{d}_6$ ,  $\delta$ ) : 2.48 (3H, s), 5.35 (2H, s), 7.00-7.40 (10H, m), 7.96 (1H, s), 8.16 (2H, d,  $J=8\text{Hz}$ )  
MS : 419  $[\text{M}+\text{H}]^+$

(3) 4-(4-Fluorophenyl)-1-(4-methoxybenzyl)-5-[4-(methylthio)phenyl]pyrazole  
IR (nujol) : 1600, 1580  $\text{cm}^{-1}$   
NMR (DMSO- $\text{d}_6$ ,  $\delta$ ) : 3.33 (3H, s), 3.79 (3H, s), 5.11 (2H, s), 6.70-7.40 (12H, m), 7.86 (1H, s)  
MS : 405  $[\text{M}+\text{H}]^+$

#### Example 12

The following compounds described in (1)-(6) were prepared in a similar manner to that of Example 2.

(1) Ethyl 1-(2,4-difluorobenzyl)-5-[4-(methylsulfonyl)phenyl]pyrazole-3-carboxylate  
white crystals  
mp : 134-137  $^{\circ}\text{C}$   
IR (KBr) : 1708, 1612, 1509, 1463  $\text{cm}^{-1}$   
NMR ( $\text{CDCl}_3$ ,  $\delta$ ) : 1.42 (3H, t,  $J=7\text{Hz}$ ), 3.09 (3H, s), 4.45 (2H, q,  $J=7\text{Hz}$ ), 6.70-7.20 (4H, m), 7.50 (2H, d,  $J=8\text{Hz}$ ), 8.00 (2H, d,  $J=8\text{Hz}$ )  
MS : 421  $[\text{M}+\text{H}]^+$

(2) 1-Benzyl-3-chloro-5-[4-(methylsulfonyl)phenyl]-

pyrazole

white crystals

mp : 135-138 °C

IR (KBr) : 1542, 1533, 1482, 1448 cm<sup>-1</sup>

5 NMR (CDCl<sub>3</sub>, δ) : 3.08 (3H, s), 5.27 (2H, s), 6.36  
(1H, s), 7.00-7.40 (5H, m), 7.49 (2H, d, J=8Hz),  
7.97 (2H, d, J=8Hz)

MS : 347 (M<sup>+</sup>), 349 (M<sup>+</sup>)

10 (3) 1-Benzyl-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)-  
phenyl]pyrazole

mp : 173-174 °C

IR (nujol) : 1550, 1530, 1310 cm<sup>-1</sup>

15 NMR (DMSO-d<sub>6</sub>, δ) : 3.28 (3H, s), 5.25 (2H, s),  
6.94-7.28 (9H, m), 7.54 (2H, d, J=8Hz), 7.93  
(1H, s), 7.98 (2H, d, J=8Hz).

MS : 407 [M+H]<sup>+</sup>

20 (4) 1-(4-Chlorobenzyl)-4-(4-fluorophenyl)-5-[4-(methyl-  
sulfonyl)phenyl]pyrazole

mp : 166-167 °C

IR (nujol) : 1605, 1550 cm<sup>-1</sup>

NMR (DMSO-d<sub>6</sub>, δ) : 3.28 (3H, s), 5.25 (2H, s), 6.98-  
7.55 (10H, m), 7.91 (2H, d, J=8Hz), 7.95 (1H, s)

25 MS : 441 [M+H]<sup>+</sup>

(5) 4-(4-Fluorophenyl)-1-(4-nitrobenzyl)-5-[4-(methyl-  
sulfonyl)phenyl]pyrazole

mp : 220-221 °C

30 IR (nujol) : 1600, 1510, 1340 cm<sup>-1</sup>

NMR (DMSO-d<sub>6</sub>, δ) : 3.32 (3H, s), 5.40 (2H, s), 7.00-  
7.20 (6H, m), 7.22 (2H, d, J=8Hz), 7.98 (2H, d,  
J=8Hz), 8.00 (1H, s), 8.14 (2H, d, J=8Hz)

MS : 452 [M+H]<sup>+</sup>

(6) 4-(4-Fluorophenyl)-1-(4-methoxybenzyl)-5-[4-(methylsulfonyl)phenyl]pyrazole

mp : 167-168 °C

IR (nujol) : 1600, 1550, 1510 cm<sup>-1</sup>

5 NMR (DMSO-d<sub>6</sub>, δ) : 3.29 (3H, s), 3.69 (3H, s), 5.17 (2H, s), 6.80-7.20 (8H, m), 7.54 (2H, d, J=8Hz), 7.90 (1H, s), 7.99 (2H, d, J=8Hz)

MS : 437 [M+H]<sup>+</sup>

10 Example 13

N-Chlorosuccinimide (25 mg) and 1-benzyl-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]pyrazole (50 mg) in acetic acid (5 ml) was stirred at 70°C for 1 hour. The reaction mixture was stirred for additional 30 minutes at 15 75°C and poured into ice-water and extracted with ethyl acetate. The organic layer was washed with water, and brine successively, dried, and concentrated to dryness. The residue was recrystallized from ethanol to afford 1-benzyl-3-chloro-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)- 20 phenyl]pyrazole (35 mg).

mp : 156-157 °C

IR (nujol) : 1600, 1550, 1510, 1300 cm<sup>-1</sup>

25 NMR (DMSO-d<sub>6</sub>, δ) : 3.26 (3H, s), 5.25 (2H, s), 7.01-7.34 (9H, m), 7.56 (2H, d, J=8Hz), 7.95 (2H, d, J=8Hz)

MS : 441 [M+H]<sup>+</sup>

Example 14

30 The following compounds described in (1)-(2) were prepared in a similar manner to that of Example 13.

(1) 3-Chloro-1-(4-chlorobenzyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]pyrazole.

mp : 148-150 °C

35 IR (nujol) : 1600 cm<sup>-1</sup>

NMR (DMSO-d<sub>6</sub>,  $\delta$ ) : 3.26 (3H, s), 5.25 (2H, s), 7.00-  
7.60 (10H, m), 7.91 (2H, d, J=8Hz)  
MS : 476 [M+H]<sup>+</sup>

- 5        (2) 3-Chloro-4-(4-fluorophenyl)-1-(4-nitorobenzyl)-5-  
          [4-(methylsulfonyl)phenyl]pyrazole  
          mp : 130-131 °C  
          IR (nujol) : 1600, 1570, 1550 cm<sup>-1</sup>  
10        NMR (DMSO-d<sub>6</sub>,  $\delta$ ) : 3.25 (3H, s), 5.42 (2H, s), 7.00-  
          7.30 (6H, m), 7.56 (2H, d, J=8Hz), 7.95 (2H, d,  
          J=8Hz), 8.17 (2H, d, J=8Hz)  
          MS : 486 [M+H]<sup>+</sup>

## C L A I M S

1. A compound of the formula :



10 wherein R<sup>1</sup> is aryl optionally substituted with  
substituent(s) selected from the group  
consisting of halogen, nitro, amino,  
esterified carboxy, carboxy, carbamoyl,  
cyano and lower alkoxy,  
R<sup>2</sup> is hydrogen, amino, halogen, estrified  
15 carboxy, carboxy, carbamoyl, cyano, or  
lower alkyl substituted with halogen,  
R<sup>3</sup> is hydrogen, aryl optionally substituted  
with halogen, or lower alkyl optionally  
substituted with hydroxy, amino or  
20 carboxy,  
R<sup>4</sup> is aryl substituted with substituent(s)  
selected from the group consisting of  
halogen, lower alkoxy, lower alkylthio,  
lower alkylsulfinyl, lower  
25 alkylsulfonyl, sulfamoyl, and lower  
alkylsulfamoyl, and  
A is lower alkylene,  
and its salt.

- 30 2. The compound according to claim 1,  
wherein A is methylene.
3. The compound according to claim 2,  
wherein R<sup>2</sup> is amino, halogen, estrified carboxy,  
35 carboxy, carbamoyl, cyano, or lower

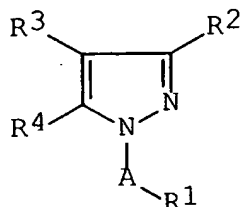
alkyl substituted with halogen, and  
R<sup>3</sup> is hydrogen.

4. The compound according to claim 2,  
5        wherein R<sup>2</sup> is hydrogen or halogen, and  
         R<sup>3</sup> is aryl optionally substituted with  
             halogen, or lower alkyl optionally  
             substituted with hydroxy, amino or  
             carboxy.

10

5. A process for preparing a compound of the formula :

15



20

wherein R<sup>1</sup> is aryl optionally substituted with  
substituent(s) selected from the group  
consisting of halogen, nitro, amino,  
esterified carboxy, carboxy, carbamoyl,  
cyano and lower alkoxy,

25

R<sup>2</sup> is hydrogen, amino, halogen, estrified  
carboxy, carboxy, carbamoyl, cyano, or  
lower alkyl substituted with halogen,  
R<sup>3</sup> is hydrogen, aryl optionally substituted  
with halogen, or lower alkyl optionally  
substituted with hydroxy, amino or  
carboxy,

30

R<sup>4</sup> is aryl substituted with substituent(s)  
selected from the group consisting of  
halogen, lower alkoxy, lower alkylthio,  
lower alkylsulfinyl, lower  
alkylsulfonyl, sulfamoyl, and lower  
alkylsulfamoyl, and

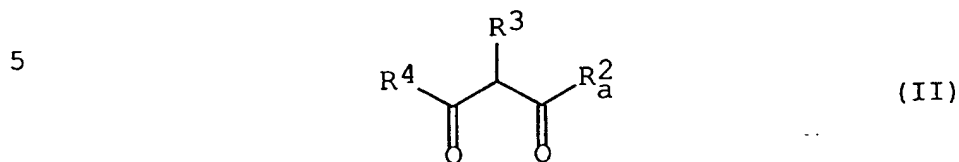
35

A is lower alkylene,

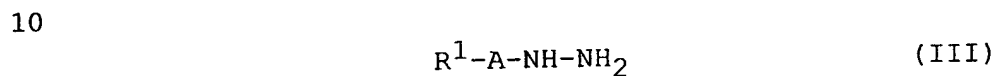


or its salt, which comprises,

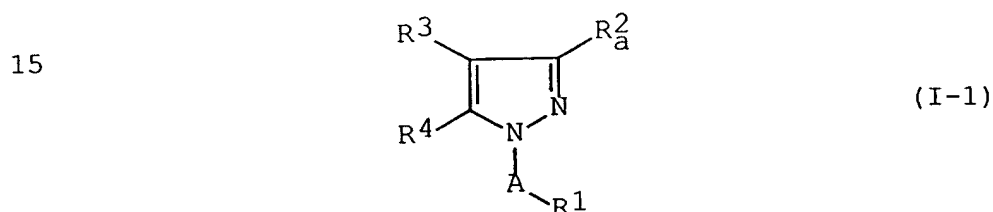
(1) reacting a compound of the formula :



or its salt, with a compound of the formula :



or its salt, to give a compound of the formula :

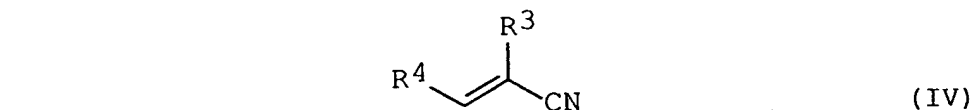


20 or its salt, in the above formulas

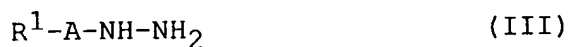
$R^1$ ,  $R^3$ ,  $R^4$  and A are each as defined above, and  $R_a^2$  is hydrogen, esterified carboxy, carbamoyl, cyano, or lower alkyl substituted with halogen,

25

(2) reacting a compound of the formula :

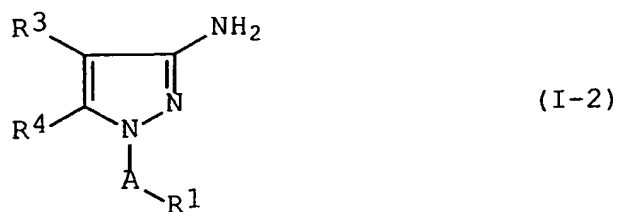


or its salt, with a compound of the formula :



35

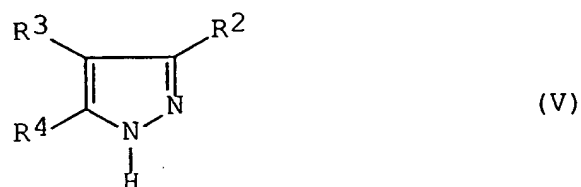
or its salt, to give a compound of the formula :



or its salt, in the above formulas

$R^1$ ,  $R^3$ ,  $R^4$  and A are each as defined above,

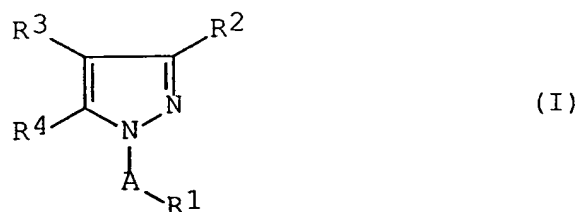
10 (3) reacting a compound of the formula :



or its salt, with a compound of the formula :



or its salt, to give a compound of the formula :



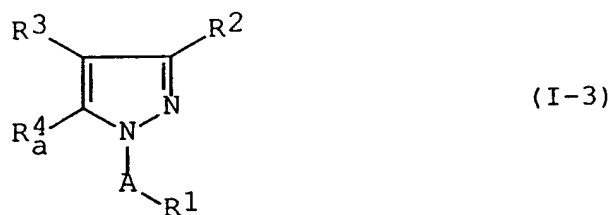
or its salt, in the above formulas

$R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$  and A are each as defined above,

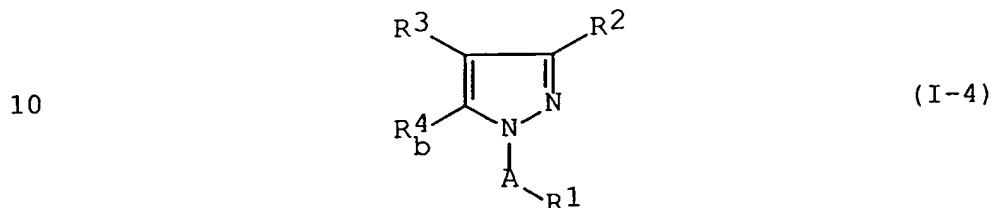
30 and

$X^1$  is leaving group,

(4) oxidizing a compound of the formula :



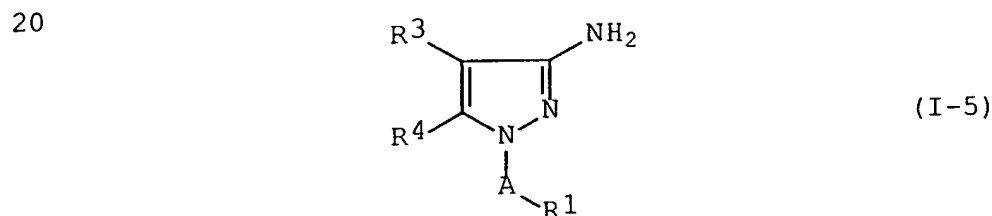
or its salt, to give a compound of the formula :



or its salt, in the above formulas

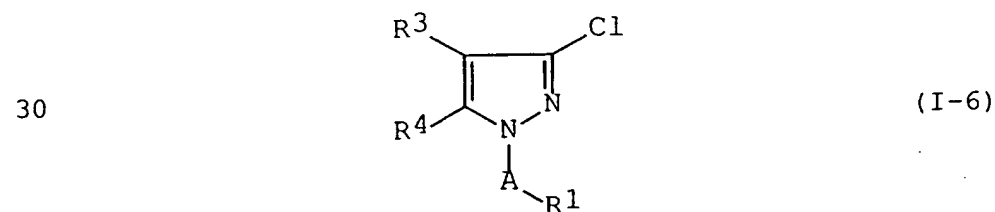
15  $R^1$ ,  $R^2$ ,  $R^3$  and A are each as defined above,  
 $R_a^4$  is aryl substituted with lower alkylthio, and  
 $R_b^4$  is aryl substituted with lower alkylsulfinyl  
or lower alkylsulfonyl,

(5) subjecting a compound of the formula :



25

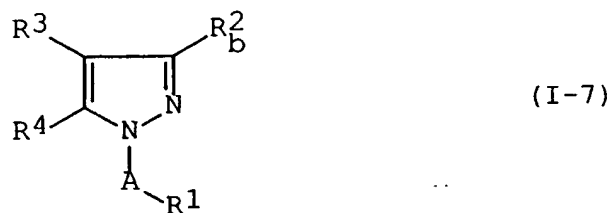
or its salt, to chlorination to give a compound of the  
formula :



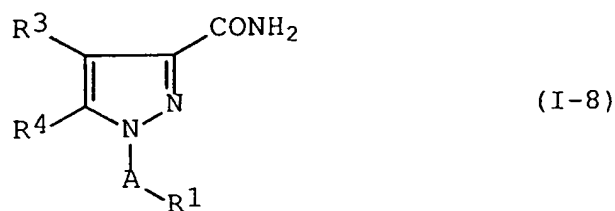
or its salt, in the above formulas

35  $R^1$ ,  $R^2$ ,  $R^3$  and A are as defined above,

(6) subjecting a compound of the formula :



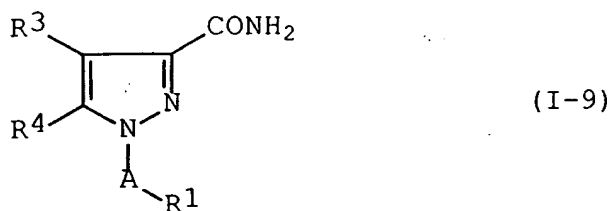
10 or its salt, to amidation reaction, to give a compound of the formula :



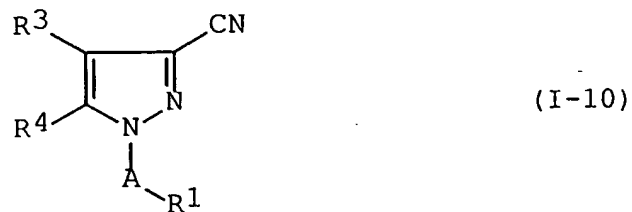
or its salt, in the above formulas

$R^1$ ,  $R^3$ ,  $R^4$  and A are each as defined above, and  $R_D^2$  is esterified carboxy or carboxy, or

(7) subjecting a compound of the formula :



or its salt, to dehydration reaction, to give a compound of the formula :



or its salt, in the above formulas

$R^1$ ,  $R^3$ ,  $R^4$  and A are each as defined above.

- 5 6. A pharmaceutical composition comprising the compound  
of claim 1, as an active ingredient, in association  
with a pharmaceutically non-toxic carrier or  
excipient.
- 10 7. A compound of claim 1 for use as a medicament.
8. COX-II inhibiting agent comprising the compound of  
claim 1.
- 15 9. A method for the treatment and/or prevention of  
inflammatory conditions, various pains, collagen  
diseases, autoimmune diseases, various immunity  
diseases, analgesic, thrombosis, cancer or  
neurodegenerative diseases which comprises administering  
an effective amount of the compound of claim 1 to  
20 human beings or animals.
- 25 10. Use of the compound of claim 1 for the manufacture of  
a medicament for treatment and/or prevention of  
inflammatory conditions, various pains, collagen  
diseases, autoimmune diseases, various immunity  
diseases, analgesic, thrombosis, cancer or  
neurodegenerative diseases in human beings or animals.

30

35

# INTERNATIONAL SEARCH REPORT

Int. Application No.

PCT/JP 98/05041

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D231/12 A61K31/415

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 97 13755 A (FUJISAWA PHARMACEUTICAL CO., LTD) 17 April 1997 see page 1 - page 2	1,6
Y	WO 95 15318 A (G.D SEARLE &CO.) 8 June 1995 cited in the application see page 4 - page 29	1,6
Y	WO 95 15316 A (G. D. SEARLE & CO.) 8 June 1995 cited in the application see page 4 - page 53, line 28	1,6
Y	EP 0 418 845 A (FUJISAWA PHARMACEUTICAL CO. LTD.) 27 March 1991 cited in the application see page 2 - page 3, line 10	1,6
-/--		

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

\* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

30 March 1999

Date of mailing of the international search report

08/04/1999

Name and mailing address of the ISA

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Authorized officer

Kyriakakou, G

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/JP 98/05041

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	DE 41 26 543 A (CHEMISCHE UND PHARMAZEUTISCHE FABRIKEN FAHLBERG-LIST GMBH) 11 February 1993 see the whole document -----	1,6
Y	US 5 486 534 A (LEN F. LEE ET AL.) 23 January 1996 see the whole document -----	1,6

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP 98/05041

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
Although claim 9  
is directed to a method of treatment of the human/animal  
body, the search has been carried out and based on the alleged  
effects of the compound/composition.
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such  
an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all  
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment  
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report  
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is  
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.



# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/JP 98/05041

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/JP 98/05041

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5486534 A		EP 0772597 A	14-05-1997
		JP 10503201 T	24-03-1998
		WO 9603385 A	08-02-1996
		US 5580985 A	03-12-1996
		US 5756530 A	26-05-1998